Published in final edited form as:
*J Am Coll Surg*. 2010 June ; 210(6): . doi:10.1016/j.jamcollsurg.2010.01.036.

# The Influence of Alcohol on Mortality in Traumatic Brain Injury

**Razvan C Opreanu, MD**[1], **Donald Kuhn, PhD**[2,3], and **Marc D Basson, MD, FACS, PhD, MBA**[1,2]

[1]Department of Surgery, Michigan State University, Lansing, MI

[2]Research Service, John D Dingell VAMC, Detroit, MI

[3]Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI

### Keywords

alcohol; mortality; traumatic brain injury

## Introduction

Traumatic brain injury (TBI) represents a major public health problem. Each year, 1.4 million people sustain TBI in the United States. 235,000 patients are hospitalized and 50,000 die. The leading cause of TBI in the general population is falls, where rates are highest among children ages 0 to 4 and among adults ages 75 or older. Falls are followed closely by motor vehicle crashes and assaults as overall causes of TBI. However, motor vehicle crashes result in the greatest number of TBI-related deaths and hospitalizations 1.

TBI injuries are extremely costly from a public health perspective since they require expenditures for hospital care, extended care, and other medical services, as well as the loss of productivity that may follow the permanent neurological consequences of TBI. For example, the Centers for Disease Control and Prevention estimated that at least 5.3 million patients have a long-term or lifelong need for help with activities of daily living because of TBI 2. As early as 1985, the annual economic burden of TBI in the United States was estimated at $37.8 billion 3, and over the past several years it has increased to almost $60 billion annually 4. One source estimated the cost of acute care and rehabilitation for new cases of TBI at $9 to $10 billion annually in 1999 5. In addition, the psychosocial burden borne by families of individuals with TBI must be taken in account even though it cannot be financially evaluated. Although not all of these figures are from the current decade, it is clear that TBI represents a prevalent and costly public health issue.

Alcohol contributes substantially to the morbidity and mortality of trauma patients, regardless of the type of injury suffered 6-9. Serum alcohol levels correlate closely with the extent of injury 10-12. In 2006, alcohol intoxication was involved in 32% of fatal motor-vehicle crashes in the United States 13. Approximately half of the alcohol-related deaths in

Corresponding Author: Marc D. Basson, MD, FACS, PhD, MBA Professor and Chair, Department of Surgery College of Human Medicine, Michigan State University 1200 East Michigan Avenue, Suite 655 Lansing, MI 48912 517-267-2486 517-267-2488 (fax) marc.basson@hc.msu.edu.



**Disclosure Information:** Nothing to disclose.

trauma occur in pre-hospital settings 9, 14. Specifically in TBI, 35-81% of the injured patients are alcohol-intoxicated 15-16 and 42% of the TBI patients were heavy drinkers before injury 16. A study from the National Trauma Databank found similar rates 17.

In contrast to the strong correlation between alcohol and pre-hospital mortality in TBI victims, the effects of alcohol on the outcome of injured patients surviving the field and admitted to the hospital is less clear. Indeed, some clinical studies surprisingly seem to suggest a beneficial effect of alcohol in injured patients with TBI. This review will analyze basic research in animal models and available clinical information to provide a realistic perspective regarding the effect of alcohol on the outcome of patients admitted to the hospital with a diagnosis of TBI. The investigational literature can be categorized into studies of the effects of low- moderate doses of alcohol in TBI animal models, investigations into the effects of high doses of alcohol in such models, and experiments directed at elucidating the mechanisms of such effects. We will consider each in turn before moving to the clinical literature.

## Experimental studies

No single experimental model of TBI can reproduce the clinical characteristics of TBI 18. Clinical TBI is complex, involving both focal and diffuse brain injuries. Moreover, most patients have secondary insults that contribute to the intricate TBI picture. For instance, systemic hemorrhage with hypotension can alter cerebral perfusion, as can intracranial bleeding that increases intracranial pressure and decreases cerebral perfusion despite the hypertension of Cushing's reflex. Along with altered cerebral perfusion, changes in levels of inflammatory cytokines, differences in oxygenation, sepsis, and many other factors contribute to the complex global physiologic derangement observed after injury.

The experimental-clinical translation of knowledge can be limited by the size and anatomic complexity of the animal model. Most experimental TBI studies use rodents. Few studies have used sheep or pigs, perhaps because of financial or animal welfare considerations. The different brain geometry among diverse species is likely a confounding factor, and findings in animal studies might not translate in the same fashion to humans 19. The mechanism by which TBI is created also varies among studies, and is necessarily more standardized and different from human TBI mechanisms. Three types of animal TBI model have been described: focal, diffuse and combined focal and diffuse brain injury 18. In most clinical cases, the human brain suffers a combined diffuse and focal form of injury. Weight drop, fluid percussion, impact acceleration or controlled cortical impact models have been created to replicate the characteristics of human TBI. These forces have been applied on the lateral cortex or over the midline. Each causes different cortical cellular pathophysiology that to a variable extent resembles the injury suffered by the human brain.

In addition, clinical studies generally focus on severe TBI, defined as a Glasgow Coma Score (GCS) below eight. In contrast, experimental studies cannot accurately replicate such severe brain injury because of the high resulting fatality rate, so most animal studies model less severe TBI. Anesthetic management also varies between clinical settings, in which propofol or benzodiazepines are commonly used after TBI, and experimental models in which anesthesia is typically applied prior to TBI because of animal welfare considerations, and in particular propofol or benzodiazepines are associated with the poorest outcomes 19.

Clinical data suggests the potential importance of demographic variables in TBI outcomes, in a manner not necessarily consistent with animal data. Such factors as gender and age have been identified as important in clinical TBI. Although the clinical opinion is that women experience better outcomes than men 20, some research studies were not able to prove this.

In one study, female patients with head injury had significantly worse intracerebral pressure reactivity and higher mortality than men 21. However, a metaanalysis yielded contradictory results with no clear conclusions on this subject 20. Although male rats exhibit better cognitive recovery than females rats 22, no gender differences were found in humans 5. Increased mortality is expected in older patients, probably because of associated comorbidities 23. Most animal studies use either healthy female or male rats with narrow age ranges. Such homogenous groups of animals cannot reflect the demographic, genetic, and clinical variability of humans injured in TBI trauma.

Differences in pharmacokinetics, dosing, or cell susceptibility to alcohol among models or species could also add to the complexity of the translation between experimental models and humans. Alcohol metabolism in the liver depends on the amount of alcohol dehydrogenase present. This varies among humans, and has genetic determinants 24. Alcohol absorption and metabolism are influenced by ingested food and gender. Alcohol is three times more slowly absorbed if there is food in the stomach 25 and women consuming similar amounts of alcohol as men are more susceptible to brain or heart muscle damage 26-27. Body weight also critically influences alcohol effects. For example, a 70kg man would have to consume three drinks of alcohol to reach a blood concentration of 0.10% (100mg/dL). A 100kg man would have to consume five drinks to reach the same blood concentration. However, these metabolic features are common to humans and variation among species would also probably be expected.

## Effects of low to moderate doses of alcohol in experimental TBI

Bearing such concerns in mind, numerous basic science studies have sought to define the effect of alcohol on the outcome of TBI in rats or swine to establish experimental models that can generate hypotheses to be further tested in humans. Although published reports seem in conflict on first reading, further analysis suggests that exposure to low doses of alcohol exerts qualitatively different results in TBI models than exposure to high dose alcohol. We will consider first the results of studies in which alcohol was administered orally or intragastrically by gavage or injected intraperitoneally at low to moderate doses (less than 1g/kg or 100 mg/dL, approximately 0.1%) (Table 1). Behavioral tests for characterization of motor or cognitive deficits 28-31, histopathology testing of neuronal layers 32 and various physiologic parameters 33-34 were used to determine the outcome in animals after administration of alcohol and experimental TBI in comparison to their respective controls.

Tureci et al. demonstrated less vacuolar degeneration in the pyramidal cell layer in rats with TBI in which alcohol was administered at low to moderate doses and concluded that alcohol may have a neuroprotective role 32. Low dose alcohol was associated with marked attenuation of immediate post-injury hyperglycolysis in rats, with more normal glucose metabolism and less reduction of the cerebral blood flow in the injury penumbra over the contusion site 34. Alcohol pretreatment lowered cytokine levels in the cortex, hippocampus and hypothalamus of rats, while serum corticosterone levels were higher after TBI induction with a low-moderate dose of alcohol compared to controls with corticosterone only 33. Both lower cytokine levels and higher corticosterone levels might contribute to alcohol neuroprotection. Indeed, less impairment of motor and cognitive functions was found in rats that had been administered low-moderate doses of alcohol after TBI generation 28-31. Thus, at least some investigations suggest that low to moderate doses of alcohol may be neuroprotective in experimental animal models of TBI.

## Effects of high doses of alcohol in experimental TBI

In contrast to the studies above, some TBI investigators have administered higher alcohol doses above 3g/kg body or 200 mg/dL by the same techniques, exceeding 0.2% blood levels (Table 2). Respiratory impairment is one of the most adverse effects associated with the use of high dose alcohol in swine 35-37. Zink et al. reported increased lactic acid in the brain and decreased organ blood flow in intoxicated swine 36. The same author separately reported multiple hemodynamic changes including decreased mean arterial pressure and cerebral blood flow after administering high dose alcohol 37. Increased brain edema and negative effects on neurobehavioral function have been described in TBI rats receiving higher doses of alcohol as opposed to TBI rats exposed without alcohol 38-39.

Exploring the apparent contrast between the effects of low and high dose alcohol on animal TBI, some researchers have employed more than one experimental group, comparing high dose alcohol with low and/or moderate dose alcohol along with control animals not receiving alcohol. Yamakami et al. demonstrated significantly increased mortality and markedly worsened neurological deficits in the high dose alcohol group compared to rats receiving low or moderate doses of alcohol 39. Gottesfeld et al. similarly reported that levels of IL1-β or TNF-α in the cortex, hippocampus or hypothalamus varied depending on whether the experimental rats received low or high dose alcohol 33. Kelly et al. observed that TBI-injured rats receiving low and moderate dose alcohol had significantly less severe behavioral outcomes compared to either rats without alcohol or rats receiving high dose alcohol 30.

## Potential mechanisms of alcohol protection in TBI

Thus, although high dose alcohol can worsen TBI, low or moderate doses of alcohol may be neuroprotective. Various mechanisms have been suggested for this neuroprotective effect, including inhibition of NMDAr (N-methyl-D-aspartic acid receptors) or sympathetic response. We will review the extant data in support of these theories.

## Blunting of N-methyl-D-aspartic acid receptors

One of the most postulated mechanisms of alcohol neuroprotection is bunting of the NMDAr. NMDAr overactivation increases levels of extracellular excitatory amino acids, glutamate and aspartate. A major release of excitatory neurotransmitters is common after TBI and is believed to be a proximate cause of a series of neurochemical sequelae of cortical injury 40-44. This chain reaction was demonstrated to promote neuronal cell death through calcium influx which activates $Ca^{2+}$-dependent enzymes that cause mitochondrial lysis 45-47. There is also evidence that the neuronal cell death occurs through sodium influx, which promotes massive cellular swelling 48-49.

This neurochemical reaction has been successfully counteracted using competitive or non-competitive antagonists targeting the binding sites of the NMDAr. Numerous basic science studies have demonstrated that the pharmacologic blockade of NMDAr improves brain metabolic status, attenuates cortical damage and overall limits neurological dysfunction after TBI 41, 50-54.

However, clinical trials of different competitive or non-competitive NMDAr antagonists 55-58 have been uniformly disappointing. None of these trials has shown any benefit for NMDAr blockade in intoxicated TBI patients. The most commonly invoked reason for this failure was the poor pharmacokinetics of these drugs and poor design of the trials 59-61. NMDAr antagonists also have adverse effects including increase in blood pressure, hallucinations or catatonia 62. These effects are encountered mainly with nonselective

NMDAr antagonists and limit the dose that can be used clinically. Hardingham et al. showed that synaptic and extra-synaptic NMDAr elicit opposing effects in hippocampal neuron cultures 63. Their study established that stimulation of synaptic NMDAr is anti-apoptotic, whereas extrasynaptic NMDAr stimulation causes loss of mitochondrial membrane potential and neuronal death. Thus, the development of selective antagonists for extrasynaptic NMDAr could prove useful in TBI in the future.

More recently, Ikonomidou and Turski 61 have offered another explanation for the failure of these clinical trials, introducing the concept of a short neuroprotective window. All of the benefits described in animal models of TBI were obtained when administration of the NMDAr antagonists was conducted prior or immediately after the TBI. In fact, neuroprotection is lost when NMDAr antagonist were started 7-10 hours after TBI 52. The overactivation of NMDAr after TBI is short-lived (less than one hour) and is followed by a more chronic upturn of receptor function that lasts more than seven days 64-65. Thus, Ikonomidou and Turski 61 suggested that the NMDAr are indeed overactivated immediately after TBI in experimental models, but only for a short period of time. It would therefore seem that the ideal system to provide neuroprotection against NMDAr overactivation in intoxicated TBI patients would be to administer the antagonists before or immediately after the TBI, when the antagonists appear most efficacious in animal studies 64. This is especially true since some published experimental studies oppose the neuroprotection concept behind the NMDAr blockage. They actually demonstrate that synaptic transmission mediated by NMDAr is essential for neuronal survival and that administration of NMDAr antagonists during the critical period after TBI, when neurodegeneration occurs, exacerbates the neuronal damage 66-67. Similarly to the NMDAr antagonists, alcohol acts by inhibiting the NMDAr synaptic current 68-72.

This short therapeutic time window may explain the failure of clinical trials of NMDAr antagonists. Infusion of NMDAr antagonists was typically started within 8-12 hours after TBI in human trials and continued for 4-6 days after the initial injury. NMDAr blockade was achieved beyond the NMDAr blockade therapeutic window with subsequent impact on the neurological outcome. In conclusion, the short-window of overactivation of NMDAr theoretically explains why low dose alcohol inhibition of NMDAr in the initial period after TBI could be neuroprotective, since the alcohol is metabolized quickly, allowing the NMDAr to return to its normal physiologic function. This same concept might also explain negative outcomes in TBI with high dose alcohol, because of the more prolonged metabolism of higher alcohol levels, proportionally to ingested amounts, in which case prolonged inhibition of NMDAr would be detrimental.

Conclusions can thus be drawn from experimental studies of alcohol impact on NMDAr and the neurophysiology of brain injury, along with data derived from clinical trials of NMDAr blockade. An alternative mode of treatment might administer NMDAr antagonists only in the immediate one hour period after TBI to block the receptor only in the short-window of overactivation of NMDAr. At the same time, consideration should be offered for the extrasynaptic NMDAr activation concept and other pitfalls associated with the use of NDMAr antagonists before further clinical trials should be restarted.

## Alcohol blunting of the adrenergic response in TBI

The sympathetic nervous system is central to the stress response to injury. An initial surge in catecholamine levels is common after TBI, followed by a prolonged hyperadrenergic state 73-78. The response of circulating hormonal levels correlates proportionally with the neurological impairment reflected by the admission GCS or Injury Severity Score 74-76. In a clinical study, Hamill et al. found that patients with severe brain injury (GCS 3-8) had a

five-fold increase in plasma norepinephrine and epinephrine levels after TBI 74. Furthermore, catecholamine levels predicted the neurological outcome and recovery in these patients. Patients who had an unchanged neurological status one week after the injury consistently showed markedly elevated plasma norepinephrine levels. Woolf et al. found that 12 out of 15 patients with twice normal norepinephrine levels and severe brain injuries (GCS 3-6) either failed to improve neurologically or died, and that norepinephrine and epinephrine levels correlated with the length of hospitalization 75. In a different study, Woolf et al. compared polytrauma patients with and without brain injuries and found that circulating norepinephrine levels significantly correlated with the severity of injury only in patients with brain injury 76.

Studies in mice have investigated the adrenergic contribution to the neurological changes that occur after TBI using β-blockers. By microPET imaging, Ley et al. demonstrated improved cerebral perfusion and decreased cerebral hypoxia in mice treated with propranolol compared to a placebo group 79. In a similar animal study, non-selective β-blockers lessened the volume of brain edema compared to placebo 80. Improved outcomes have been also reported in retrospective clinical studies with the use of β-blockers in TBI, with greatest effect in the elderly and more severely injured. These studies provide Level III evidence that β-blockers improve mortality in injured patients with TBI 81-85.

There is good evidence that alcohol intoxication blunts the sympathetic surge that is observed after TBI since increased alcohol levels are associated with decreased circulating norepinephrine and epinephrine response and improved GCS scores in patients with TBI 86-87. However, only retrospective studies have addressed the potential beneficial effect of sympathetic blockade in TBI. The potential benefits of β-blockers in the prevention of TBI complications and death could be better defined by prospective studies in the future.

## Clinical studies of the effect of alcohol in TBI

There has recently been increased interest in research on the effects of alcohol in specific TBI populations, driven by a combination of attractive basic science data, the failure of most clinical trials, and the contradictory results of retrospective studies of mortality in alcohol-intoxicated patients with multiple injuries with or without TBI. It is important to distinguish here between studies that examined mortality in patients with or without TBI and other associated injuries and studies that were limited to patients with TBI with or without associated injuries.

When the study population comprised traumatized patients that did not necessarily have TBI, various researchers have demonstrated increased, decreased or no difference in mortality in intoxicated patients admitted to the hospital. For instance, Luna et al. found a fourfold increase in mortality in intoxicated compared with unintoxicated motorcyclists 88. Moreover, the protective effect of the helmet was lost in intoxicated patients. Similarly, in a more heterogeneous population with polytrauma resulting from motor vehicle crashes, falls or sports injuries, Pories et al. reported increased mortality in intoxicated patients 11.

In contrast, some researchers reported decreased mortality among intoxicated patients with any type of injury, not necessarily TBI. Plurad et al. found decreased mortality in victims of motor vehicle crashes with high dose compared to low dose alcohol 89. Other researchers have also reported decreased mortality after alcohol intoxication with various mechanisms of injuries such as assaults, burns or stabbing resulting in a high preponderance of blunt over penetrating injuries, and again without necessarily including TBI 90-91.

In the setting of some reports of increased mortality and some of decreased mortality in intoxicated trauma patients, it is important to recognize that many investigators have found

no statistically significant differences in mortality of alcohol intoxicated injured patients in either direction 92-96. These studies included patients with any type of injury and not necessarily with TBI. For example, Jurkovich et al. performed a subgroup analysis based on time of death, i.e. in the field, trauma bay, within 24 hours of admission, or after longer hospitalization 93. Although there were was no evidence that alcohol affected mortality in these groups of patients, subgroup analysis based on mechanism of injury, magnitude of hemodynamic or inflammatory alterations, or type of TBI could be more revealing.

In contrast to these studies of patients with any type of injury, some researchers have aimed to test mortality in a specific cohort of patients with TBI without or with other associated injuries. Studies restricted to TBI patients still demonstrate some inconsistencies, but may be more readily understandable (Table 3). One of the first studies of the association between alcohol and mortality in TBI was published in 2004 by Alexander et al. This study found no impact of alcohol levels at admission on mortality 97. However, the small sample size of this study may have obscured a significant difference between the patient groups, if present. Tien et al in 2006 were the first to report significant differences in mortality in TBI patients depending upon alcohol levels 98. In this seminal study, the authors divided the patients into three groups based on admission alcohol levels. These groups were no alcohol (0 mg/dL), low-moderate alcohol (less than 230 mg/dL), and high alcohol (above 230 mg/dL). The low-moderate alcohol group exhibited better survival than the no alcohol group. In contrast, compared to the same no alcohol reference group, the high alcohol group demonstrated worse survival rates. O'Phelan et al. reported similar findings in 2008 in a more diverse population including patients with substance abuse as well as alcohol intoxication 99.

Shandro et al. found no statistically significant difference in mortality among patient groups with TBI in 2009, but the data did demonstrate a clear trend toward a beneficial outcome and lower mortality in intoxicated patients with higher blood alcohol levels 100, and so this study may be also consistent with the concept of alcohol neuroprotectivity in clinical TBI. In contrast to previous studies, these authors did not exclude patients who did not have blood alcohol levels measured at admission. Instead, they used a multiple imputation technique to represent the missing data, trying to exclude the bias pertaining to missing values using a modern statistical technique. This method might have contributed to their indefinite result. Salim et al. recently published two other important studies, one using data from the national trauma data bank, and the other focusing on patients from a major trauma center. In each case, alcohol-intoxicated patients regardless of blood levels were compared with patients who tested negative for alcohol. Each study found lower mortality in intoxicated patients with TBI 17, 101. Thus, clinical studies tend to suggest a protective effect of pre-traumatic alcohol intoxication on TBI outcomes, but such studies also have significant limitations.

## Influence of pre-TBI alcohol on neuropsychological testing

Besides mortality and morbidity, neuropsychological outcomes have also been investigated in patients with TBI and prior alcohol use. Patients with alcohol abuse and/or alcohol dependence were followed for different periods of time after TBI and neuropsychological/cognitive outcomes were compared with those of sober patients with TBI. Most researchers who have studied individuals with alcohol abuse and alcohol dependence prior to TBI have found inferior performance on neuropsychological/cognitive testing in alcohol-intoxicated patients with TBI 102-105. In contrast, Lange et al. reported that sober patients with TBI performed more poorly in neuropsychological/cognitive testing than intoxicated patients 106. A key difference is that Lange et al. enrolled only alcohol-intoxicated patients at the time of injury and without any history of alcohol dependence. It is important to separate these types of patients into different groups based on the presence of alcohol abuse or dependence since their outcomes may be dissimilar. Whether alcohol intoxication at the time

of injury can mitigate the neurological effects of subsequent TBI remains to be determined. In contrast, such neurologic sequelae may promote self-medication with alcohol in TBI patients. Such patients may need alternative strategies to ameliorate their TBI if alcohol cessation is to be achieved.

## Limitations of Clinical Studies

Understanding the limitations of the clinical studies that have investigated the effects of alcohol on mortality in TBI patients is important to design more effective research in the future. Such clinical studies are unavoidably retrospective since prospective trials offering alcohol to an intervention group would probably be unethical unless strong evidence can be developed first for a protective effect. The same guidelines for control of confounding variables should be considered with regard to medications or other potential treatments. For example, future research designs should take into consideration the potential neuroprotective affect of β-blockers.

One discrepancy among extant clinical studies is the definition of the study groups. Some researchers have ascertained only the presence or absence of blood alcohol, while others 98, 100 have categorized patients into upon the magnitude of their blood alcohol levels. Future studies should incorporate these considerations in their design for the same purpose as stated above.

Another concern about the inclusion criteria for many previous studies is that some patients did not have blood alcohol levels measured at admission and therefore were excluded from analysis in most studies. The selection bias introduced by the exclusion of this type of data would likely be eliminated by prospective measurements of blood alcohol levels in injured patients. Trauma centers that have incorporated routine alcohol determination in injured patients into routine screening guidelines would be able to perform such a research study without this particular type of bias.

It is also important to distinguish acute alcohol intoxication from chronic alcoholism. Chronic alcoholism is associated with immunosuppression 107-109, and increased risk of infection, particularly pneumonia because of impairment of lung cytokine production 110. Chronic alcoholism might thus be an important factor in mortality and morbidity of patients with TBI that should be considered in these types of research. Serum levels of γ-glutamyltransferase closely correlate with chronic alcohol consumption 111-112 and may be useful in differentiating chronic alcoholism from the trauma victim with acute intoxication.

Most clinical studies on the effects of pre-existing alcohol on TBI have used mortality as the primary endpoint. Other outcome variables including intensive care unit and hospital length of stay, ventilator days or complications have also been considered. Unfortunately, no specific functional neurological outcomes were addressed in these studies. This represents another opportunity for further research.

Another important limitation of these studies is the lack of analysis based on specific types of injuries. Blunt or penetrating injuries might have different outcomes in terms of morbidity and mortality which could be specific to each type. It is probably also important to seek specific outcome patterns based on the location of the injury, i.e. frontal, temporal or occipital lobes. Moreover, interplay with other associated injuries can obscure the influence of alcohol on TBI, and should be carefully tracked in future studies.

## Alcohol consumption after TBI

Patterns of alcohol consumption following TBI have recently received considerably more attention in the literature. In general, after TBI, alcohol drinking varies over time. Early in the recovery period, alcohol use tends to decline 113-116. Indeed, 20-80% of the patients with previous alcohol abuse problems tend to stop abusing alcohol for at least a short period of time after TBI 113-114, 117. However, many of these patients that initially overcome alcohol abuse after TBI then relapse into the alcohol abuse patterns of their pre-injury period. Indeed, heavy drinking increases with time after TBI 114, 116, 118. Moreover, it appears that a history of alcohol drinking prior to injury is a strong predictor of heavy drinking after TBI 119. Not unexpectedly, patients with less education tend to have higher relapse drinking rates 102. In contrast, higher alcohol levels on admission also may predict a decrease in drinking after TBI 116. A more severe TBI, as defined by initial GCS, seems to also predict decreased drinking after TBI. The last two variables may actually be covariates since a higher alcohol level is associated with more severe injuries in trauma patients 10-12. These findings could be explained by the psychological effect of the injury or limited finances of these patients. In addition, more of the patients with initially lower GCS would seem likely to need placement in extended care facilities where alcohol availability would be limited.

The period of time over which these patients abstain from alcohol is short,. varying from one month to one year after TBI 116. Secondary prevention programs would probably have the greatest success when implemented during this opportunity window, as described by Bombardier et al. 115, especially since during this period of time, patients frequently contemplate changing their alcohol habits 120.

Consumption of alcohol after TBI is associated with several complications. Patients are at increased risk of recurrent TBI upon returning to their pre-injury alcohol habits 121. Continuation of alcohol drinking after TBI is also associated with more atrophy of the cerebral cortex 122, development of post-traumatic seizures 123-124 and deterioration of behavioral functioning 125-126. Overall, the data suggests that secondary prevention of subsequent complications resulting either directly from recurrent TBI or from effects of alcohol on a previously injured cortex, should be implemented early after TBI.

## Conclusion

Considerable progress has been made to elucidate the role of alcohol in TBI by both experimental and clinical studies. That the resulting data is somewhat contradictory is probably not surprising, considering the complexity of the pathophysiologic response that accompanies TBI and any other associated injuries. Secondary prevention of alcohol abuse after TBI is as important as primary prevention and should be emphasized in the first month after the injury. There is a substantial need for further clinical and experimental research with regards to the mechanisms responsible for the neurophysiology of TBI. For clinical studies in particular, a systematic approach might be beneficial in which details about possible confounders are taken into account. Potential mechanisms of alcohol effects on TBI including blockage of NMDAr and sympathetic surge need to be investigated in detail to be able to identify new opportunities for treatments to decrease mortality and morbidity in clinical settings. In the interim, screening for alcohol intake in trauma patients, good clinical care to prevent TBI, and subsequent counseling regarding the dangers of further alcohol intake are definite weapons available to the practicing trauma surgeon today.

## References


1. Langlois, JA.; Rutland-Brown, W.; Thomas, KE. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; Atlanta (GA): 2004.
2. Thurman DJ, Alverson C, Dunn KA, et al. Traumatic brain injury in the United States: A public health perspective. J Head Trauma Rehabil. 1999; 14:602–615. [PubMed: 10671706]
3. Max W, MacKenzie EJ, Rice DP. Head injuries: costs and consequences. J Head trauma Rehabil. 1991; 6:76–91.
4. Finkelstein, E.; Corso, PS.; Miller, TR. The incidence and economic burden of injuries in the United States. Oxford University Press; New York: 2006. p. xiii
5. Moore DW, Ashman TA, Cantor JB, et al. Does gender influence cognitive outcome after traumatic brain injury? Neuropsychol Rehabil. 2009:1–15. [PubMed: 18609020]
6. NHTSA. The Economic Impact of Motor Vehicle Crashes. Dept of Transportation (US), National Highway Traffic Safety Administration (NHTSA); Washington, DC: 2000. Available at: http://www.dot.gov/safety.html [Accessed November 07, 2009]
7. The Economic Impact of Motor Vehicle Crashes 2000. Dept of Transportation, National Highway Traffic Safety Administration; Washington, DC: 2000. http://www-nrd.nhtsa.dot.gov/Pubs/ [Accessed November 07, 2009]
8. U.S. Dept. of Transportation, National Highway Traffic Safety Division. Traffic Safety Facts 1996:Alcohol. National Center for Statistics & Analysis, Research & Development; Washington, DC: 1997.
9. Stewart RM, Myers JG, Dent DL, et al. Seven hundred fifty-three consecutive deaths in a level I trauma center: the argument for injury prevention. J Trauma. 2003; 54:66–70. discussion 70-61. [PubMed: 12544901]
10. Fabbri A, Marchesini G, Morselli-Labate AM, et al. Positive blood alcohol concentration and road accidents. A prospective study in an Italian emergency department. Emerg Med J. 2002; 19:210–214. [PubMed: 11971829]
11. Pories SE, Gamelli RL, Vacek P, et al. Intoxication and injury. J Trauma. 1992; 32:60–64. [PubMed: 1732576]
12. Waller PF, Stewart JR, Hansen AR, et al. The potentiating effects of alcohol on driver injury. JAMA. 1986; 256:1461–1466. [PubMed: 3747064]
13. National Highway Traffic Safety Administration. Traffic Safety Facts. 2006.
14. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. J Trauma. 1995; 38:185–193. [PubMed: 7869433]
15. Corrigan JD. Substance abuse as a mediating factor in outcome from traumatic brain injury. Arch Phys Med Rehabil. 1995; 76:302–309. [PubMed: 7717829]
16. Kolakowsky-Hayner SA, Gourley EV 3rd, Kreutzer JS, et al. Pre-injury substance abuse among persons with brain injury and persons with spinal cord injury. Brain Inj. 1999; 13:571–581. [PubMed: 10901686]
17. Salim A, Ley EJ, Cryer HG, et al. Positive serum ethanol level and mortality in moderate to severe traumatic brain injury. Arch Surg. 2009; 144:865–871. [PubMed: 19797113]
18. Morales DM, Marklund N, Lebold D, et al. Experimental models of traumatic brain injury: do we really need to build a better mousetrap? Neuroscience. 2005; 136:971–989. [PubMed: 16242846]
19. Statler KD, Jenkins LW, Dixon CE, et al. The simple model versus the super model: translating experimental traumatic brain injury research to the bedside. J Neurotrauma. 2001; 18:1195–1206. [PubMed: 11721738]
20. Farace E, Alves WM. Do women fare worse? A metaanalysis of gender differences in outcome after traumatic brain injury. Neurosurg Focus. 2000; 8:e6. [PubMed: 16924776]
21. Czosnyka M, Radolovich D, Balestreri M, et al. Gender-related differences in intracranial hypertension and outcome after traumatic brain injury. Acta Neurochir Suppl. 2008; 102:25–28. [PubMed: 19388282]

22. Wagner AK, Kline AE, Sokoloski J, et al. Intervention with environmental enrichment after experimental brain trauma enhances cognitive recovery in male but not female rats. Neurosci Lett. 2002; 334:165–168. [PubMed: 12453621]
23. Hukkelhoven CW, Steyerberg EW, Rampen AJ, et al. Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. J Neurosurg. 2003; 99:666–673. [PubMed: 14567601]
24. Bosron WF, Ehrig T, Li TK. Genetic factors in alcohol metabolism and alcoholism. Semin Liver Dis. 1993; 13:126–135. [PubMed: 8337601]
25. Jones AW, Jonsson KA. Food-induced lowering of blood-ethanol profiles and increased rate of elimination immediately after a meal. J Forensic Sci. 1994; 39:1084–1093. [PubMed: 8064267]
26. Urbano-Marquez A, Estruch R, Fernandez-Sola J, et al. The greater risk of alcoholic cardiomyopathy and myopathy in women compared with men. JAMA. 1995; 274:149–154. [PubMed: 7596003]
27. Nixon SJ. Cognitive deficits in alcoholic women. Alcohol Health & Research World. 1994; 18:228–232.
28. Dash PK, Moore AN, Moody MR, et al. Post-trauma administration of caffeine plus ethanol reduces contusion volume and improves working memory in rats. J Neurotrauma. 2004; 21:1573–1583. [PubMed: 15684650]
29. Janis LS, Hoane MR, Conde D, et al. Acute ethanol administration reduces the cognitive deficits associated with traumatic brain injury in rats. J Neurotrauma. 1998; 15:105–115. [PubMed: 9512086]
30. Kelly DF, Lee SM, Pinanong PA, Hovda DA. Paradoxical effects of acute ethanolism in experimental brain injury. J Neurosurg. 1997; 86:876–882. [PubMed: 9126906]
31. Taylor AN, Romeo HE, Beylin AV, et al. Alcohol consumption in traumatic brain injury: attenuation of TBI-induced hyperthermia and neurocognitive deficits. J Neurotrauma. 2002; 19:1597–1608. [PubMed: 12542860]
32. Tureci E, Dashti R, Tanriverdi T, et al. Acute ethanol intoxication in a model of traumatic brain injury: the protective role of moderate doses demonstrated by immunoreactivity of synaptophysin in hippocampal neurons. Neurol Res. 2004; 26:108–112. [PubMed: 14977068]
33. Gottesfeld Z, Moore AN, Dash PK. Acute ethanol intake attenuates inflammatory cytokines after brain injury in rats: a possible role for corticosterone. J Neurotrauma. 2002; 19:317–326. [PubMed: 11939499]
34. Kelly DF, Kozlowski DA, Haddad E, et al. Ethanol reduces metabolic uncoupling following experimental head injury. J Neurotrauma. 2000; 17:261–272. [PubMed: 10776911]
35. Zink BJ, Feustel PJ. Effects of ethanol on respiratory function in traumatic brain injury. J Neurosurg. 1995; 82:822–828. [PubMed: 7714608]
36. Zink BJ, Schultz CH, Wang X, et al. Effects of ethanol on brain lactate in experimental traumatic brain injury with hemorrhagic shock. Brain Res. 1999; 837:1–7. [PubMed: 10433981]
37. Zink BJ, Walsh RF, Feustel PJ. Effects of ethanol in traumatic brain injury. J Neurotrauma. 1993; 10:275–286. [PubMed: 8258840]
38. Katada R, Nishitani Y, Honmou O, et al. Prior ethanol injection promotes brain edema after traumatic brain injury: evidence for poor prognosis for intoxicated patients. J Neurotrauma. 2009
39. Yamakami I, Vink R, Faden AI, et al. Effects of acute ethanol intoxication on experimental brain injury in the rat: neurobehavioral and phosphorus-31 nuclear magnetic resonance spectroscopy studies. J Neurosurg. 1995; 82:813–821. [PubMed: 7714607]
40. Bondoli A, Barbi S, Camaioni D, et al. Plasma and cerebrospinal fluid free amino acid concentration in post-traumatic cerebral oedema in patients with shock. Resuscitation. 1981; 9:119–124. [PubMed: 7255951]
41. Faden AI, Demediuk P, Panter SS, Vink R. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. Science. 1989; 244:798–800. [PubMed: 2567056]
42. Katayama Y, Becker DP, Tamura T, Hovda DA. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. J Neurosurg. 1990; 73:889–900. [PubMed: 1977896]

43. Nilsson P, Hillered L, Ponten U, Ungerstedt U. Changes in cortical extracellular levels of energy-related metabolites and amino acids following concussive brain injury in rats. J Cereb Blood Flow Metab. 1990; 10:631–637. [PubMed: 2384536]
44. Panter SS, Yum SW, Faden AI. Alteration in extracellular amino acids after traumatic spinal cord injury. Ann Neurol. 1990; 27:96–99. [PubMed: 2301932]
45. Garthwaite G, Hajos F, Garthwaite J. Ionic requirements for neurotoxic effects of excitatory amino acid analogues in rat cerebellar slices. Neuroscience. 1986; 18:437–447. [PubMed: 3526174]
46. Choi DW. Ionic dependence of glutamate neurotoxicity. J Neurosci. 1987; 7:369–379. [PubMed: 2880938]
47. Choi DW. Glutamate neurotoxicity in cortical cell culture is calcium dependent. Neurosci Lett. 1985; 58:293–297. [PubMed: 2413399]
48. Rothman SM. The neurotoxicity of excitatory amino acids is produced by passive chloride influx. J Neurosci. 1985; 5:1483–1489. [PubMed: 3925091]
49. Rothman S. Synaptic release of excitatory amino acid neurotransmitter mediates anoxic neuronal death. J Neurosci. 1984; 4:1884–1891. [PubMed: 6737044]
50. McIntosh TK, Vink R, Soares H, et al. Effect of noncompetitive blockade of N-methyl-D-aspartate receptors on the neurochemical sequelae of experimental brain injury. J Neurochem. 1990; 55:1170–1179. [PubMed: 2168932]
51. McIntosh TK, Vink R, Soares H, et al. Effects of the N-methyl-D-aspartate receptor blocker MK-801 on neurologic function after experimental brain injury. J Neurotrauma. 1989; 6:247–259. [PubMed: 2559212]
52. Bernert H, Turski L. Traumatic brain damage prevented by the non-N-methyl-D-aspartate antagonist 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo[f] quinoxaline. Proc Natl Acad Sci U S A. 1996; 93:5235–5240. [PubMed: 8643559]
53. Dempsey RJ, Baskaya MK, Dogan A. Attenuation of brain edema, blood-brain barrier breakdown, and injury volume by ifenprodil, a polyamine-site N-methyl-D-aspartate receptor antagonist, after experimental traumatic brain injury in rats. Neurosurgery. 2000; 47:399–404. discussion 404-396. [PubMed: 10942013]
54. Ikonomidou C, Qin Y, Labruyere J, et al. Prevention of trauma-induced neurodegeneration in infant rat brain. Pediatr Res. 1996; 39:1020–1027. [PubMed: 8725264]
55. Morris GF, Bullock R, Marshall SB, et al. Failure of the competitive N-methyl-D-aspartate antagonist Selfotel (CGS 19755) in the treatment of severe head injury: results of two phase III clinical trials. The Selfotel Investigators. J Neurosurg. 1999; 91:737–743. [PubMed: 10541229]
56. Yurkewicz L, Weaver J, Bullock MR, Marshall LF. The effect of the selective NMDA receptor antagonist traxoprodil in the treatment of traumatic brain injury. J Neurotrauma. 2005; 22:1428–1443. [PubMed: 16379581]
57. Merchant RE, Bullock MR, Carmack CA, et al. A double-blind, placebo-controlled study of the safety, tolerability and pharmacokinetics of CP-101,606 in patients with a mild or moderate traumatic brain injury. Ann N Y Acad Sci. 1999; 890:42–50. [PubMed: 10668412]
58. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. J Neurotrauma. 2002; 19:503–557. [PubMed: 12042091]
59. Lee JM, Zipfel GJ, Choi DW. The changing landscape of ischaemic brain injury mechanisms. Nature. 1999; 399:A7–14. [PubMed: 10392575]
60. Arciniegas DB. Designing clinical trials to improve neurobehavioral outcome after traumatic brain injury: from bench to bedside. Crit Care Med. 2009; 37:784–785. [PubMed: 19325389]
61. Ikonomidou C, Turski L. Why did NMDA receptor antagonists fail clinical trials for stroke and traumatic brain injury? Lancet Neurol. 2002; 1:383–386. [PubMed: 12849400]
62. Kemp JA, McKernan RM. NMDA receptor pathways as drug targets. Nat Neurosci. 2002; 5(Suppl):1039–1042. [PubMed: 12403981]
63. Hardingham GE, Fukunaga Y, Bading H. Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. Nat Neurosci. 2002; 5:405–414. [PubMed: 11953750]

64. Biegon A, Fry PA, Paden CM, et al. Dynamic changes in N-methyl-D-aspartate receptors after closed head injury in mice: Implications for treatment of neurological and cognitive deficits. Proc Natl Acad Sci U S A. 2004; 101:5117–5122. [PubMed: 15044697]
65. Benveniste H, Drejer J, Schousboe A, Diemer NH. Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. J Neurochem. 1984; 43:1369–1374. [PubMed: 6149259]
66. Ikonomidou C, Stefovska V, Turski L. Neuronal death enhanced by N-methyl-D-aspartate antagonists. Proc Natl Acad Sci U S A. 2000; 97:12885–12890. [PubMed: 11058158]
67. Young D, Lawlor PA, Leone P, et al. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. Nat Med. 1999; 5:448–453. [PubMed: 10202938]
68. Calton JL, Wilson WA, Moore SD. Magnesium-dependent inhibition of N-methyl-D-aspartate receptor-mediated synaptic transmission by ethanol. J Pharmacol Exp Ther. 1998; 287:1015–1019. [PubMed: 9864287]
69. Lovinger DM, White G, Weight FF. Ethanol inhibits NMDA-activated ion current in hippocampal neurons. Science. 1989; 243:1721–1724. [PubMed: 2467382]
70. Morrisett RA, Martin D, Oetting TA, et al. Ethanol and magnesium ions inhibit N-methyl-D-aspartate-mediated synaptic potentials in an interactive manner. Neuropharmacology. 1991; 30:1173–1178. [PubMed: 1775222]
71. Weight FF, Lovinger DM, White G. Peoples RW. Alcohol and anesthetic actions on excitatory amino acid-activated ion channels. Ann N Y Acad Sci. 1991; 625:97–107. [PubMed: 1711821]
72. White G, Lovinger DM, Weight FF. Ethanol inhibits NMDA-activated current but does not alter GABA-activated current in an isolated adult mammalian neuron. Brain Res. 1990; 507:332–336. [PubMed: 2186844]
73. Clifton GL, Ziegler MG, Grossman RG. Circulating catecholamines and sympathetic activity after head injury. Neurosurgery. 1981; 8:10–14. [PubMed: 7207763]
74. Hamill RW, Woolf PD, McDonald JV, et al. Catecholamines predict outcome in traumatic brain injury. Ann Neurol. 1987; 21:438–443. [PubMed: 3592639]
75. Woolf PD, Hamill RW, Lee LA, et al. The predictive value of catecholamines in assessing outcome in traumatic brain injury. J Neurosurg. 1987; 66:875–882. [PubMed: 3572517]
76. Woolf PD, McDonald JV, Feliciano DV, et al. The catecholamine response to multisystem trauma. Arch Surg. 1992; 127:899–903. [PubMed: 1642533]
77. Mautes AE, Muller M, Cortbus F, et al. Alterations of norepinephrine levels in plasma and CSF of patients after traumatic brain injury in relation to disruption of the blood-brain barrier. Acta Neurochir (Wien). 2001; 143:51–57. discussion 57-58. [PubMed: 11345718]
78. Woolf PD, Hamill RW, Lee LA, McDonald JV. Free and total catecholamines in critical illness. Am J Physiol. 1988; 254:E287–291. [PubMed: 3348389]
79. Ley EJ, Scehnet J, Park R, et al. The in vivo effect of propranolol on cerebral perfusion and hypoxia after traumatic brain injury. J Trauma. 2009; 66:154–159. discussion 159-161. [PubMed: 19131818]
80. Liu MY. Protective effects of propranolol on experimentally head-injured mouse brains. J Formos Med Assoc. 1995; 94:386–390. [PubMed: 7549561]
81. Riordan WP Jr. Cotton BA, Norris PR, et al. Beta-blocker exposure in patients with severe traumatic brain injury (TBI) and cardiac uncoupling. J Trauma. 2007; 63:503–510. discussion 510-501. [PubMed: 18073593]
82. Cotton BA, Snodgrass KB, Fleming SB, et al. Beta-blocker exposure is associated with improved survival after severe traumatic brain injury. J Trauma. 2007; 62:26–33. discussion 33-25. [PubMed: 17215730]
83. Inaba K, Teixeira PG, David JS, et al. Beta-blockers in isolated blunt head injury. J Am Coll Surg. 2008; 206:432–438. [PubMed: 18308212]
84. Arbabi S, Campion EM, Hemmila MR, et al. Beta-blocker use is associated with improved outcomes in adult trauma patients. J Trauma. 2007; 62:56–61. discussion 61-52. [PubMed: 17215733]
85. Salim A, Hadjizacharia P, Brown C, et al. Significance of troponin elevation after severe traumatic brain injury. J Trauma. 2008; 64:46–52. [PubMed: 18188098]

86. Woolf PD, Cox C, Kelly M, et al. Alcohol intoxication blunts sympatho-adrenal activation following brain injury. Alcohol Clin Exp Res. 1990; 14:205–209. [PubMed: 2190486]

87. Woolf PD, Cox C, McDonald JV, et al. Effects of intoxication on the catecholamine response to multisystem injury. J Trauma. 1991; 31:1271–1275. discussion 1275-1276. [PubMed: 1920559]

88. Luna GK, Maier RV, Sowder L, et al. The influence of ethanol intoxication on outcome of injured motorcyclists. J Trauma. 1984; 24:695–700. [PubMed: 6471133]

89. Plurad D, Demetriades D, Gruzinski G, et al. Motor vehicle crashes: The association of alcohol consumption with the type and severity of injuries and outcomes. J Emerg Med. 2008

90. Blondell RD, Looney SW, Krieg CL, Spain DA. A comparison of alcohol-positive and alcohol-negative trauma patients. J Stud Alcohol. 2002; 63:380–383. [PubMed: 12086139]

91. Ward RE, Flynn TC, Miller PW, Blaisdell WF. Effects of ethanol ingestion on the severity and outcome of trauma. Am J Surg. 1982; 144:153–157. [PubMed: 7091524]

92. Huth JF, Maier RV, Simonowitz DA, Herman CM. Effect of acute ethanolism on the hospital course and outcome of injured automobile drivers. J Trauma. 1983; 23:494–498. [PubMed: 6864840]

93. Jurkovich GJ, Rivara FP, Gurney JG, et al. The effect of acute alcohol intoxication and chronic alcohol abuse on outcome from trauma. JAMA. 1993; 270:51–56. [PubMed: 8510296]

94. Shih HC, Hu SC, Yang CC, et al. Alcohol intoxication increases morbidity in drivers involved in motor vehicle accidents. Am J Emerg Med. 2003; 21:91–94. [PubMed: 12671806]

95. Thal ER, Bost RO, Anderson RJ. Effects of alcohol and other drugs on traumatized patients. Arch Surg. 1985; 120:708–712. [PubMed: 4004557]

96. Jehle D, Cottington E. Effect of alcohol consumption on outcome of pedestrian victims. Ann Emerg Med. 1988; 17:953–956. [PubMed: 3415067]

97. Alexander S, Kerr ME, Yonas H, Marion DW. The effects of admission alcohol level on cerebral blood flow and outcomes after severe traumatic brain injury. J Neurotrauma. 2004; 21:575–583. [PubMed: 15165365]

98. Tien HC, Tremblay LN, Rizoli SB, et al. Association between alcohol and mortality in patients with severe traumatic head injury. Arch Surg. 2006; 141:1185–1191. discussion 1192. [PubMed: 17178960]

99. O'Phelan K, McArthur DL, Chang CW, et al. The impact of substance abuse on mortality in patients with severe traumatic brain injury. J Trauma. 2008; 65:674–677. [PubMed: 18784583]

100. Shandro JR, Rivara FP, Wang J, et al. Alcohol and risk of mortality in patients with traumatic brain injury. J Trauma. 2009; 66:1584–1590. [PubMed: 19509618]

101. Salim A, Teixeira P, Ley EJ, et al. Serum ethanol levels: predictor of survival aer severe traumatic brain injury. J Trauma. 2009; 67:697–703. [PubMed: 19820573]

102. Jorge RE, Starkstein SE, Arndt S, et al. Alcohol misuse and mood disorders following traumatic brain injury. Arch Gen Psychiatry. 2005; 62:742–749. [PubMed: 15997015]

103. Bombardier CH, Thurber CA. Blood alcohol level and early cognitive status after traumatic brain injury. Brain Inj. 1998; 12:725–734. [PubMed: 9755364]

104. Kelly MP, Johnson CT, Knoller N, et al. Substance abuse, traumatic brain injury and neuropsychological outcome. Brain Inj. 1997; 11:391–402. [PubMed: 9171925]

105. Tate PS, Freed DM, Bombardier CH, et al. Traumatic brain injury: influence of blood alcohol level on post-acute cognitive function. Brain Inj. 1999; 13:767–784. [PubMed: 10576461]

106. Lange RT, Iverson GL, Franzen MD. Effects of day-of-injury alcohol intoxication on neuropsychological outcome in the acute recovery period following traumatic brain injury. Arch Clin Neuropsychol. 2008; 23:809–822. [PubMed: 18768292]

107. Roberts PJ, Segal AW. The digestion of bacterial macromolecules by phagocytic cells: the effect of mepacrine and ethanol. Immunology. 1987; 62:581–586. [PubMed: 2448226]

108. Nelson S, Bagby GJ, Bainton BG, Summer WR. The effects of acute and chronic alcoholism on tumor necrosis factor and the inflammatory response. J Infect Dis. 1989; 160:422–429. [PubMed: 2668425]

109. Wagner F, Fink R, Hart R, et al. Ethanol inhibits interferon-gamma secretion by human peripheral lymphocytes. J Stud Alcohol. 1992; 53:277–280. [PubMed: 1583907]

110. Nelson S, Bagby G, Andresen J, et al. The effects of ethanol, tumor necrosis factor, and granulocyte colony-stimulating factor on lung antibacterial defenses. Adv Exp Med Biol. 1991; 288:245–253. [PubMed: 1719751]
111. Papoz L, Weill J, L'Hoste J, et al. Biological markers of alcohol intake among 4796 subjects injured in accidents. Br Med J (Clin Res Ed). 1986; 292:1234–1237.
112. Patel S, O'Gorman P. Serum enzyme levels in alcoholism and drug dependency. J Clin Pathol. 1975; 28:414–417. [PubMed: 239023]
113. Hibbard MR, Uysal S, Kepler K, et al. Axis I psychopathology in individuals with traumatic brain injury. J Head Trauma Rehabil. 1998; 13:24–39. [PubMed: 9651237]
114. Corrigan JD, Lamb-Hart GL, Rust E. A programme of intervention for substance abuse following traumatic brain injury. Brain Inj. 1995; 9:221–236. [PubMed: 7606236]
115. Bombardier CH, Temkin NR, Machamer J, Dikmen SS. The natural history of drinking and alcohol-related problems after traumatic brain injury. Arch Phys Med Rehabil. 2003; 84:185–191. [PubMed: 12601648]
116. Dikmen SS, Machamer JE, Donovan DM, et al. Alcohol use before and after traumatic head injury. Ann Emerg Med. 1995; 26:167–176. [PubMed: 7618779]
117. Kreutzer JS, Doherty K, Harris J, Zasler N. Alcohol use among persons with traumatic brain injury. J Head Trauma Rehabil. 1990; 5:9–20.
118. Kreutzer JS, Witol AD, Marwitz JH. Alcohol and drug use among young persons with traumatic brain injury. J Learn Disabil. 1996; 29:643–651. [PubMed: 8942308]
119. Horner MD, Ferguson PL, Selassie AW, et al. Patterns of alcohol use 1 year after traumatic brain injury: a population-based, epidemiological study. J Int Neuropsychol Soc. 2005; 11:322–330. [PubMed: 15892908]
120. Bombardier CH, Ehde D, Kilmer J. Readiness to change alcohol drinking habits after traumatic brain injury. Arch Phys Med Rehabil. 1997; 78:592–596. [PubMed: 9196466]
121. Salcido R, Costich JF. Recurrent traumatic brain injury. Brain Inj. 1992; 6:293–298. [PubMed: 1581750]
122. Ronty H, Ahonen A, Tolonen U, et al. Cerebral trauma and alcohol abuse. Eur J Clin Invest. 1993; 23:182–187. [PubMed: 8477793]
123. Freedland ES, McMicken DB. Alcohol-related seizures, Part I: Pathophysiology, differential diagnosis, and evaluation. J Emerg Med. 1993; 11:463–473. [PubMed: 8228111]
124. Freedland ES, McMicken DB, D'Onofrio G. Alcohol and trauma. Emerg Med Clin North Am. 1993; 11:225–239. [PubMed: 8432251]
125. Dunlop TW, Udvarhelyi GB, Stedem AF, et al. Comparison of patients with and without emotional/behavioral deterioration during the first year after traumatic brain injury. J Neuropsychiatry Clin Neurosci. 1991; 3:150–156. [PubMed: 1821228]
126. Bales JW, Wagner AK, Kline AE, Dixon CE. Persistent cognitive dysfunction after traumatic brain injury: A dopamine hypothesis. Neurosci Biobehav Rev. 2009; 33:981–1003. [PubMed: 19580914]

## Table 1

Experimental Studies of the Impact of Alcohol Intoxication (Low to Moderate Doses) on Outcomes of Subsequent Traumatic Brain Injury

| First author | Year | Animal model | Main findings |
|---|---|---|---|
| Dash 28 | 2004 | Rats | Caffeine and alcohol reduced cortical tissue loss and improved working memory |
| Janis 29 | 1998 | Rats | Alcohol provided better results on memory probe tests in rats, reducing the severity of cognitive impairments caused by |
| Kelly 30 | 1997 | Rats | Less mortality and severe beam-walking impairment in the low and moderate dose alcohol groups |
| Taylor 31 | 2002 | Rats | Alcohol attenuated induced hyperthermia and deficits in spatial learning |
| Tureci 32 | 2004 | Rats | Less vacuolar degeneration in the pyramidal cell layer in the low and moderate dose alcohol groups |
| Gottesfeld 33 | 2002 | Rats | Decrease in proinflammatory cytokine production |
| Kelly 34 | 2000 | Rats | Less reduction in cerebral blood flow and a decreased degree of uncoupling between glucose metabolism and cerebral blood flow |

## Table 2

Experimental Studies of the Impact of Alcohol Intoxication (High Doses) on Outcomes of Subsequent Traumatic Brain Injury

| First author | Year | Animal model | Main findings |
|---|---|---|---|
| Zink 35 | 1995 | Pigs | Impairment in respiratory control following TBI |
| Zink 36 | 1999 | Swine | Increased in concentration of brain and cerebral venous blood lactate |
| Zink. 37 | 1993 | Swine | Increased hemodynamic (decreased mean arterial and cerebral perfusion pressure) and respiratory depression |
| Katada 38 | 2009 | Rats | Increased volume of cytotoxic brain edema after TBI |
| Yamakami 39 | 1995 | Rats | Significantly increased mortality |

## Table 3

Clinical Studies of the Impact of Alcohol Intoxication on Outcomes of Subsequent Traumatic Brain Injury

| First author | Year | No. pts included | No. pts excluded | Patient groups | Mortality outcomes |
|---|---|---|---|---|---|
| Alexander 97 | 2004 | 80 (42%) | 108 (58%) | Three groups<br>0 mg/dL; 1-100 mg/dL; >100 mg/dL | No difference in mortality among the three groups of patients |
| Tien 98 | 2006 | 3675 (89.7%) | 424 (10.3%) | Three groups<br>0 mg/dL; 0-230 mg/dL; >230 mg/dL | Increased mortality in the >230 mg/dL group when compared to the 0 mg/dL group<br>Decreased mortality in the 0-230 mg/dL group when compared to the 0 mg/dL group |
| O'Phelan 99 | 2008 | 255 (52.8%) | 228 (47.2%) | Two groups<br>Alcohol negative or positive * | Decreased mortality in the alcohol positive group |
| Salim 101 | 2009 | 482 (47%) | 543 (53%) | Two groups<br>Alcohol negative or positive | Decreased mortality in the alcohol positive group |
| Salim 17 | 2009 | 38019 (52.6%) | 34275 (47.4%) | Two groups<br>Alcohol negative or positive | Decreased mortality in the alcohol positive group |
| Shandro 100 † | 2009 | 836 (54.6%) | 693 (45.4%) | Three groups<br>0.1-100 mg/dL; 101-230 mg/dL; >230 mg/dL | No significant difference in mortality among these groups, but a clear trend toward lower mortality in the 101-230 mg/dL and >230 mg/dL groups |

All studies had a retrospective design and used abbreviated injury score of three or more for head to select for severe traumatic brain injury. The number of patients included represents the final population used in the analysis. In these studies, patients were excluded due to missing data on blood alcohol levels.

* In addition to alcohol intoxication, the patients enrolled in this study were under the influence of other various substances (methamphetamine, cocaine or marijuana).

† The study by Shandro and colleagues did not demonstrate a statistical significant difference between the different groups of patients but did show a trend toward lower mortality in patients with higher alcohol levels.